REMARKS/ ARGUMENTS

Applicant has carefully studied the final Examiner's Action mailed April 1, 2010, having a shortened statutory period for response set to expire July 1, 2010. The amendment appearing above and these explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Claim Rejections - 35 U.S.C. § 112

Office has rejected claims 1-5, 17, and 20 under 35 U.S.C § 112, first paragraph, for failing to enable the claimed invention. The Office found that the specification enables reducing NSAID gastric lesion and reducing gastric ulceration from NSAIDs through co-administration of an MAO inhibitor.[1] The Office further found the specification does not enable agents of claim 2, which the Office found includes agents which are not anti-inflammatory compounds. Applicant has amended claim 2, removing compounds that are not related to anti-inflammatory agents.

The Office also provided that "'prevention' is synonymous with a treatment having absolute success. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as gastrointestinal ulceration, the specification is viewed as lacking enablement."[2] Applicant points out that the term prevention means "to keep from happening" or "to keep (someone from doing something); hinder; impede[.]"[3] Applicant respectfully requests the Office provide documentation to support the finding that prevention requires absolute success. Applicant notes that NSAIDs produced large amounts of gastric damage, as seen in Table 3 of the specification.[4] Co-administration of MAO inhibitor reduced gastric damage from 100% down to 21-40% for 100 mg/kg MAO inhibitor, and 1-20% for 100 mg/kg MAO inhibitor. These results show that co-administration of MAO inhibitors with anti-inflammatory agents prevents damage, reducing damage to 1-40% the amount caused by the anti-inflammatory agent alone, based on the amount of MAO inhibitor.

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[1] Page 2 of the final Office Action, dated April 1, 2010.
[2] Page 3 of the final Office Action, dated April 1, 2010.
[3] http://www.thefreedictionary.com/prevent (last accessed June 29, 2010); http://www.merriam-webster.com/dictionary/prevent (last accessed June 29, 2010) ("to hold or keep back **:** HINDER, STOP —often used with *from*").
[4] Page 25, Table 3; Page 23, lines 8-10.

To determine whether a disclosure adequately enables an invention, a series of factors have been established, including the breadth of claims, nature of the invention, state of prior art, relative skill in the art, predictability in the art, the amount of direction or guidance, presence of working examples, and amount of experimentation needed.[5] 35 U.S.C. § 112 is satisfied if "the specification contains within it *a connotation* of how to use" the invention or the use is known in the art.[6]

Breadth of Claims

The Office contends the claims are overbroad, as the claims cover preventing gastrointestinal side effects which occur from many different causes, such as bacterial infection, NSAID damage, cigarettes, or no identifiable causative agent.[7] Applicant submits that claim 1 is drawn to "preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs [,]" not preventing all ulceration. Therefore, it is submitted that the claims do not touch upon ulcers from cigarettes or bacterial infection. While other agents may impact the ulceration of an individual, the claims are drawn to the ulceration effects from anti-inflammatory drugs, and claim 1 is limited to this very specific effect of the anti-inflammatory drugs.

Applicant reasserts that anti-inflammatory drug effects are generally mediated through cyclooxygenase (COX) enzyme inhibition,[8] thereby reducing eicosanoid and prostaglandin synthesis.[9] Nonselective COX inhibition causes adverse effects, including gastrointestinal (GI) problems like gastroduodenal ulcers and gastrointestinal bleeding.[10] Further, anti-inflammatory treatment results in neutrophil adhesion, mucosal blood flow reduction, mucous diminishment, and free radical production.[11] Because anti-inflammatory drugs typically rely on the same pathway, at least partly, the side effects of anti-inflammatory drugs may be prevented and treated

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[5] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).
[6] MPEP 2164.01(c). (Emphasis added).
[7] Page 3 of the final Office Action, dated April 1, 2010.
[8] Page 2 of the Application; J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, "Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme," Proc. Nat. Acad. Sci., 1992, 89, 3917-3921, page 3919, column 2.
[9] Page 2 of the Application; J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, "Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme," Proc. Nat. Acad. Sci., 1992, 89, 3917-3921, page 3919, column 2.; Solomon, D., "Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American college of rheumatology white paper", Arthritis Rheum. 2008 Aug 15;59(8):1058-73, page 1059, column 1.
[10] Unknown author, "Balancing Cardiovascular Rishs and Gastrointestinal Outcomes in NSAID Users; A Report from a Symposium held During the American College of Gastroenterology 71st Annual Meeting and Postgraduate Course," Gastroent. & Hepat., Mar. 2007, 3:3, 4-13, page 4, column 1.

by targeting such common pathways. Anti-inflammatory drug effects are reversed by MAO inhibitors, such as deprenyl, through effects including free radical scavenging, antioxidant properties, stimulation of antioxidant enzyme expression, endothelial protection, vasodilation, enhanced blood flow, and stimulation of nitrogen oxide synthase.[12] The specification shows administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reverses gastrointestinal lesions by one week pretreatment.[13]

Nature of the Invention, State of the Art and Predictability

The Office found the claims drawn to a method of preventing, reducing and reversing the gastrointestinal ulceration from anti-inflammatory drugs and enhancing the beneficial effects of the anti-inflammatory compounds.[14] The Office then found the nature of the invention is complex, as it encompasses prevention of ulcer development.[15] Further, the claims were found not to be enabled because of the complex nature of the invention.[16] Applicant respectfully points out that the complex nature of the invention is one of the factors that must be considered in determining enablement. Further, the specification provides examples of MAO inhibitors preventing anti-inflammatory drug side effect damage. For example, administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reversed gastrointestinal lesions by one week pretreatment.[17] In similar experiments conducted over 7 days, pretreatment with L-deprenyl or propargylamine prevented formation of gastric lesions and reversed lesions.[18]

NSAID-induced ulceration and damage is "largely caused by blocking COX-1 and COX-2, and other prostaglandin-independent mechanisms, such as H_2S and NO reduction.[19] COX-1 inhibition is believed to result in microvascular damage, restricting blood flow and causing tissue hypoxia and decreased mucosal resistance,[20] causing increased mucosal permeability and

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[11] Page 4 of the Application.
[12] Pages 17-18 of the Application.
[13] Example 5, pages 22-23; table 3, page 25 of the Application.
[14] Pages 3-4 of the final Office Action, dated April 1, 2010.
[15] Page 4 of the final Office Action, dated April 1, 2010.
[16] Page 4 of the final Office Action, dated April 1, 2010.
[17] Example 5, pages 22-23; table 3, page 25 of the Application.
[18] Example 5, pages 22-23; table 3, page 25 of the Application.
[19] Yuan, et al. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9; page 82, column 1-2; Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3, page 2, column 1; page 3, Table 1.
[20] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1; page 7, column 2.

myeloperoxidase activity, eventually causing gastric lesions.[21] NSAIDs increase endothelin-converting enzyme-1 (ECE-1) activity, upregulating endothelin-1 (ET-1), which results in suppressed cNOS and endothelial nitric oxide leading to loss of mucosal integrity in rats."[22] Acid diffusion through the mucosal barrier further destroys tissue and results in deeper necrosis and ulceration.[23]

NO is responsible for maintenance of gastric epithelium integrity and the mucus barrier,[24] and helps decrease acid secretion from parietal cells.[25] Importantly, "reduction in blood flow … thought to be the mechanism most responsible for NSAID-induced GI injury,"[26] caused by ICAM expression resulting in neutrophil adherence to the vascular endothelium.[27] Anti-inflammatory drug effects are reversed by MAO inhibitors, such as deprenyl, through effects including free radical scavenging, antioxidant properties, stimulation of antioxidant enzyme expression, endothelial protection, vasodilation, enhanced blood flow, and stimulation of nitrogen oxide synthase.[28] The use of MAO inhibitors therefore shows a reduction in adverse effects of anti-inflammatory drugs, namely neutrophil adhesion, mucosal blood flow reduction, mucous diminishment, and free radical production.[29]

The Office states that the state of the art provides 60% of peptic ulcers are caused by *H. pylori*, making the practice unpredictable in terms of the role of anti-inflammatory agents. Applicant notes that the claims are drawn to the effects of anti-inflammatory agents, not other

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[21] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1.
[22] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 2.
[23] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 2.
[24] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column1; page 2, column 2.
[25] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column 2.
[26] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 496, column 2; Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 1, column 1; page 2, column 1.
[27] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 496, column 2; Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 3, column 1. See also, Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 5, column 1 (COX-1 depletion results in decrease in gastric mucosal blood flow, whereas COX-2 depletion promotes leucocyte adherence, and suppression of either COX enzyme in impaired gastric musocal- such as NO synthesis suppression or acid challenge- is ulcerogenic).
[28] Pages 17-18 of the Application.
[29] Page 4 of the Application.

agents. Additionally, NSAIDs are linked to gastrointestinal damage, regardless of whether other agents are also damaging the GI tract. The present invention addresses preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs, not the prevention, reduction, and reversal of all gastrointestinal ulceration. The application provides for protection of gastrointestinal mucous after one pretreatment and reversed gastrointestinal lesions by one week pretreatment.[30]

Amount of Direction or Guidance/ Working examples

The Office states that the guidance provided by the specification on the how to administer the compounds to prevent ulceration is minimal.[31] The specification was found to disclose analgesic and anti-inflammatory activities of aspirin and indomethacin, combined with propargylamine or l-deprenyl,[32] and for the treatment rather than prevention of ulcers.[33]

Applicant notes that the NSAID-MAOi compounds were administered to the mice, and the MAO inhibitor attached to the NSAID attenuated gastric toxicity.[34] The specification provides that NSAID gastropathology is a result of gastric microcirculation[35] and that MAO inhibitors may be administered at 0.1 to 10 times the NSAID dose of 0.1-500 mg/kg.[36] L-deprenyl shows a reduction in gastric lesion damage at 100 mg/kg and at 200 mg/kg; 21-40% and 1-20% of lesions in mice treated only with anti-inflammatory, respectively.[37,38] The specification also includes working examples of the invention in reducing gastric ulceration, illustrating that the administration of MAO inhibitor provides a protective effect for cells.[39]

Not every embodiment or procedure to practice the invention need be disclosed for the invention to be enabled.[40] The application discloses that MAO inhibitors L-deprenyl and propargylamine effectively prevent formation of gastric lesions and reverse lesion progression during prolonged treatment, as seen in table 3.[41] The claims do not require all side effects of

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[30] Pages 17-18; Example 5, pages 22-23; table 3, page 25 of the Application.
[31] Page 5 of the final Office Action, dated April 1, 2010.
[32] Page 5 of the final Office Action, dated April 1, 2010.
[33] Page 6 of the final Office Action, dated April 1, 2010.
[34] Pages 22-23; Table 3 of the Application.
[35] Page 4 of the Application.
[36] Page 19 of the Application.
[37] Page 25, table 3 of the Application.
[38] Example 5, pages 22-23; table 3, page 25 of the Application.
[39] Page 25, table 3 of the Application (Providing lesion reduction at provided dosages for L-deprenyl and propargyline).
[40] MPEP2164.08
[41] Page 23; table 3 of the Application.

each drug be prevented, but rather for enablement the invention must prevent or treat at least one side effect of the drugs. L-deprenyl and propargylamine treatment is shown effective in preventing and reducing NSAID side effects. SAIDs act through the same pathway as NSAIDs, by inhibiting COX, to produce an anti-inflammatory effect. Though NSAIDs and SAIDs have different side effects, both anti-inflammatory treatments utilize COX-dependent pathways. As such, the application discloses at least one example of preventing the side effects of NSAIDs and SAIDs. Therefore, NSAIDs and SAIDs may be effectively treated by compounds that target such similar pathways and the claims are consistent with the scope of the disclosure.

A specification does not require working examples, but may utilize prophetic examples to describe the invention based on "predicted results."[42] The specification does include working examples of the invention in reducing platelet activation and reducing gastric ulceration.[43] Applicant respectfully submits that the administration of an MAO inhibitor was found to (1) prevent the occurrence of ulceration following anti-inflammatory treatment;[44] and (2) reverse the ulceration cause by previous anti-inflammatory treatment.[45] Cardiovascular events, caused by anti-inflammatory treatment, develop due to the prothrombic activity of the drugs, causing platelet coagulation and resulting in cardiovascular events like congestive heart failure, stroke, vascular death, and myocardial infarction.[46] Leukocyte activation and adhesion is known in the art,[47] and pretreatment of L-deprenyl (5 mg/kg) inhibited leukocyte activation induced by TNF-α,[48] thereby preventing cardiovascular events caused by anti-inflammatory drugs. Additionally, the specification discloses L-deprenyl and propargylamine reduces and prevents gastric lesions,[49] commonly caused by anti-inflammatory drug treatment. Thus, the specification illustrates that the treatment of an MAO inhibitor effectively prevents, reduces, and reverses the effects of anti-inflammatory drugs.

Amount of Experimentation Required

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[42] MPEP 2164.02. Citing *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).
[43] Examples 3 and 5, pages 21-23 of the Application.
[44] See, page 22-23 of the Application (for example, "Pretreatment with l-deprenyl provided protection against the NSAID induced gastric lesion.")
[45] See, page 22-23 of the Application (for example, "The gastric lesions were also reversed by daily administration of l-deprenyl for 7 days.")
[46] *Id.* at page 5-6.
[47] See, T. Thomas, J. Rhodin, L. Clark, A. Garces, "Progestin Initiate Adverse Events of Menopausal Estrogen Therapy," Climacteric, Dec. 2003; 6(4):293-301.
[48] Example 3, page 21 of the Application.
[49] Example 5, page 23; table 3, page 25 of the Application.

The Office found that to practice the invention, one would need to envision a combination of carrier, compound dosage, treatment duration, administration route and test the compound for effect.[50] Applicant respectfully submits that the administration of an MAO inhibitor was found to (1) prevent the occurrence of ulceration following anti-inflammatory treatment;[51] and (2) reverse the ulceration cause by previous anti-inflammatory treatment.[52]

"Enablement is not precluded by the necessity for some experimentation *such as routine screening*."[53] Varying the timing for treatment administration and/or the dosage of anti-inflammatory and MAO inhibitor is essentially a drug screening process. According to *Wands*, screening is within the routine practice of the medicinal and scientific arts.[54] Based on the prior work performed in the art, the level of skill in the art, and the disclosure, the invention is adequately described for prevention, reduction, and reversion of the side effects of anti-inflammatory drugs.

NSAID-induced ulceration and damage, which occurs throughout the GI tract,[55] is caused mainly by blocking COX-1 and COX-2, and other prostaglandin-independent mechanisms, such as H_2S and NO reduction.[56] This causes increased mucosal permeability and myeloperoxidase activity, eventually causing gastric lesions.[57] NSAIDs increase endothelin-converting enzyme-1 (ECE-1) activity, upregulating endothelin-1 (ET-1), which results in suppressed cNOS and endothelial nitric oxide leading to loss of mucosal integrity in rats."[58] NO is responsible for maintenance of gastric epithelium integrity and the mucus barrier,[59] and helps

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[50] Page 6 of the final Office Action, dated April 1, 2010.
[51] See, page 22-23 of the Application (for example, "Pretreatment with l-deprenyl provided protection against the NSAID induced gastric lesion.")
[52] See, page 22-23 of the Application (for example, "The gastric lesions were also reversed by daily administration of l-deprenyl for 7 days.")
[53] *In re Wands*, 858 F.2d at 736-737. (Emphasis added).
[54] See generally, *In re Wands*, 858 F.2d at 739.
[55] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 495, column 2 (noting additional damage in such locations as small-bowel).
[56] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3, page 2, column 1; page 3, Table 1; Yuan, et al. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9; page 82, column 1-2.
[57] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1.
[58] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 2.
[59] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column1; page 2, column 2.

decrease acid secretion from parietal cells.[60] The present invention provides that the MAO inhibitors act by, among other actions, stimulating constitutive neuronal and endothelial nitric oxide synthase (cNOS and eNOS), [61] thereby upregulating NO.

35 U.S.C. § 112 is satisfied if "the specification contains within it *a connotation* of how to use" the invention or the use is known in the art.[62] Office bears the initial burden to show the specification does not enable the claimed invention. The medicinal and scientific arts are highly skilled arts, as noted by the Office.[63] The specification provides guidance as to the timing and dosage of MAO inhibitor, as refers to the prior art (PDR) for calculations on patient dosages. The specification does include working examples of the invention in gastrointestinal ulceration prevention and reduction/ reversion, as well as prevention of cardiovascular events. As such, based on the prior art, skill of the ordinary artisan, and disclosure, the invention is adequately described to allow a skilled artisan to use the invention for treatment for preventing, reducing and reversing the toxic effects of anti-inflammatory drugs. The *Wands* factors indicate the invention may be performed without undue experimentation, as discussed *supra*. Accordingly, it is respectfully requested that the rejection of claims 1-5, 7, and 20 be withdrawn by the Office.

Claim Rejections - 35 U.S.C. § 102

Claims 1-5, 17, and 20 stand rejected under 35 U.S.C. § 102(b) as anticipated by *Lai* (U.S. Pat. No. 5,916,910). The Office found *Lai* discusses administering a conjugate composition of NSAID and NO scavenger and MAO inhibitor.[64] Applicant respectfully points out that *Lai* provides "conjugates of physiologically compatible nitric oxide scavengers (e.g., dithiocarbamates (DC)) and pharmacologically active agents (e.g., NSAIDS)."[65] Further, the pharmacologically active agents may be a myriad of compounds, such as NSAIDS,[66]

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[60] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column 2.
[61] Page 17 of the Application.
[62] MPEP 2164.01(c). (Emphasis added).
[63] Page 5 of the final Office Action, dated April 1, 2010.
[64] Pages 7-8 of the final Office Action, dated April 1, 2010.
[65] Lai (U.S. Pat. No. 5,916,910); column 2, lines 63-65.
[66] Lai (U.S. Pat. No. 5,916,910); column 7, lines 43-57.

analgesics,[67] cyclooxygenase inhibitors,[68] and MAO B inhibitors, such as selegiline and Parkinyl.[69] Applicant notes claim 1 provides, in part

> administering to a subject an effective amount of monoamine oxidase (MAO) inhibitor;
> wherein the anti-inflammatory drug and MAO inhibitor are chemically linked, physically mixed or administered separately[.]

It is submitted that *Lai* does not disclose administering an anti-inflammatory with an MAO inhibitor, but rather a NO scavenger with some other compound, such as an MAO inhibitor. Conversely, the present invention administers an MAO inhibitor with an anti-inflammatory.[70] The MAO inhibitor, among other actions, stimulates the production of cNOS, thereby enhancing production of nitric oxide.[71] Thus, it is submitted that the MAO inhibitor cannot be a NO scavenger, as the MAO inhibitor increases the amount of NO rather than reduces the amount of NO, which is the expected result of a NO scavenger. Applicant also notes that "[a] device which does not operate on the same principle cannot be an anticipation."[72] *Lai* therefore fails to disclose the elements of the claim and cannot anticipate the invention.

Accordingly, Applicant respectfully requests the Office withdraw the 35 U.S.C. § 102(b) rejection of claims 1-5, 17, and 20.

Claim Rejections - 35 U.S.C. § 103

Claims 1-5, 17, and 20

Claims 1-5, 7, 17, and 20 stand rejected under 35 U.S.C. § 103(a) as anticipated by in view of *Glavin, et al.* (Neurosci. Ltrs., 1986) and *Lianping, et al.* (Dig. Disease Sci., 1990). The Office states that *Glavin, et al.* discloses an association between duodenal ulceration and dopamine deficiency,[73] and *Lianping, et al.* provides MAO inhibitors can reduce stress-induced gastric ulceration through inhibition of gastrin release.[74] The Office then noted that the

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[67] Lai (U.S. Pat. No. 5,916,910); column 7, line 58 to column 8, line 3.
[68] Lai (U.S. Pat. No. 5,916,910); column 11, lines 35-46.
[69] Lai (U.S. Pat. No. 5,916,910); column 15, lines 13-14.
[70] See, amended claim 1, presented herein.
[71] See, claim 5 of the originally-filed Application.
[72] *Los Alamitos Sugar Co. v. Carroll*, 173 F. 280, 284 (9th Cir. 1909). *Nat'l Business Systems, Inc. v. AM Int'l, Inc.*, 743 F.2d 1227, 223 U.S.P.Q. 1011 (7th Cir. 1985) (citing Saunders v. Air-Flo Co., 646 F.2d 1201, 1203 (7th Cir. 1981)).
[73] Page 9 of the final Office Action, dated April 1, 2010.
[74] Page 9 of the final Office Action, dated April 1, 2010.

references do not disclose preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs, but found it would be obvious to prevent the toxic effects of anti-inflammatory drugs because *Glavin, et al.* discloses that L-deprenyl prevents duodenal ulceration in MPTP-treated rats and *Lianping, et al.* discloses inhibiting ulceration in stress-induced rats, administered MAO inhibitors. Applicant submits that the combination fails to obviate the claimed invention because (1) the combination of *Glavin, et al.* and *Lianping, et al.*, as well as the rationale propounded to support obviousness, fail to address NSAID-induced ulceration; (2) the combination of references fail to disclose the claimed invention; and (3) the Office has not propounded a rationale support for the finding of obviousness.

The combination of *Glavin, et al.* and *Lianping, et al.* fail to obviate the claimed invention, because the combination and rationale fails to address NSAID-induced ulceration. Applicant submits that the art considers sources of gastrointestinal damage to be different from stress-induced ulceration and dopamine-depletion-induced ulceration. Applicant's respectfully submits that the etymologies of stress-induced ulceration, dopamine-deficient ulceration, and NSAID-induced ulceration are different, comprising different mechanisms of onset and treatment. In rejecting the claims, the Office relied on ulceration caused by stress and dopamine-depletion.[75] As noted by the Office, the claims are drawn to method for preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs by administering a chemically-linked anti-inflammatory drug and MAO inhibitor.

NSAID-induced ulceration and damage, which occurs throughout the GI tract,[76] is "largely caused by the inhibition of COX1 and its role in normal mucosal defense mechanisms … and also through the inhibition of thromboxane A_2, which compromises platelet function and results in gastrointestinal bleeding."[77] NSAID damage occurs through topical and systemic effects, systemic are mainly by blocking COX-1 and COX-2, and other prostaglandin-independent mechanisms, such as H_2S and NO reduction,[78] which "are two endogenously

[75] Pages 9-10 of the final Office Action, dated April 1, 2010.
[76] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 495, column 2 (noting additional damage in such locations as small-bowel).
[77] Yuan, et al. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9; page 82, column 1-2.
[78] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3, page 2, column 1; page 3, Table 1.

generated gaseous mediators important in maintaining gastric mucosal integrity that share many biological effects with prostaglandins."[79]

COX-1 inhibition is believed to result in microvascular damage, restricting blood flow and causing tissue hypoxia and decreased mucosal resistance.[80] This causes increased mucosal permeability and myeloperoxidase activity, eventually causing gastric lesions.[81] NSAIDs increase endothelin-converting enzyme-1 (ECE-1) activity, upregulating endothelin-1 (ET-1), which results in suppressed cNOS and endothelial nitric oxide leading to loss of mucosal integrity in rats."[82] Acid diffusion through the mucosal barrier further destroys tissue and results in deeper necrosis and ulceration.[83]

NO is responsible for maintenance of gastric epithelium integrity and the mucus barrier,[84] and helps decrease acid secretion from parietal cells.[85] Importantly, "reduction in blood flow … thought to be the mechanism most responsible for NSAID-induced GI injury,"[86] caused by ICAM expression resulting in neutrophil adherence to the vascular endothelium[87] This is supported by studies which found "[m]ost NSAID-induced ulcers develop in the gastric antrum, which is also the site of greatest reduction in gastric mucosal blood flow. It has been suggested that this is because of focal ischaemia impairing the ability of the mucosa to withstand

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[79] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 2 (also noting that eNOS and nNOS produce NO which functions in mucosal repair and ulcer healing depending on amount of NO); page 9, column 1 (noting an increase in NO during gastric ulcer healing).

[80] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1; page 7, column 2.

[81] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1.

[82] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 2.

[83] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 2.

[84] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column1; page 2, column 2.

[85] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column 2.

[86] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 496, column 2; Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 1, column 1; page 2, column 1.

[87] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 496, column 2; Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 3, column 1. See also, Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 5, column 1 (COX-1 depletion results in decrease in gastric mucosal blood flow, whereas COX-2 depletion promotes leucocyte adherence, and suppression of either COX enzyme in impaired gastric musocal- such as NO synthesis suppression or acid challenge- is ulcerogenic).

acid back diffusion leading to tissue injury."[88] Further, *Kim, et al.* showed decreased antral blood blow significantly correlated with gastric mucosal injury.[89]

> "Microvascular damage plays an early and critical role in the pathogenesis of NSAID-induced ulcers, underscoring the fact that the mucosal microvascular response is possibly the most important component of mucosal defence [sic]. The hyperaemic response to gastric acid is predominantly mediated by extrinsic sensory primary nerves … [resulting in] *subsequent nitric oxide-mediated vasodilation increasing submucosal blood flow*." [90]

NO can limit or prevent blood flow reduction and block adherence of neutrophils to the vascular endothelium associated with NSAIDs.[91] This is supported by newly-developed COX-inhibiting, NO-donating drugs (CINODs), which have been developed in response to NSAID toxicity. The compoudns couple NO to an NSAID to improve GI safety.[92] Studies have found significantly reduced gastric damage compared to NSAIDs, when administered twice daily,[93] and increased blood flow and improved mucosal integrity.[94]

Conversely, stress induced ulcers are superficial and "clearly distinguished from … ulcers induced by drugs and from activation of a preexistent ulcer."[95] These stress-induced ulcerations do not possess an identified, definitive causative agent,[96] though "prolonged exposure to stress induces low-grade mucosal inflammation, leads to ultrastructural epithelial abnormalities and alters bacterial-host interactions including bacterial translocation[,]"[97] and

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[88] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 7, column 2.
[89] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 1.
[90] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 7, column 2 (emphasis added).
[91] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 4, column 1.
[92] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 1, column 2.
[93] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 4, column 1 (NO-naproxen (naproxcinod) compared to naproxen); page 4 column 2 to page 5, column 1.
[94] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 4, column 2 (NO-fluriprofen compared to fluriprofen).
[95] Silen, et al. The pathophysiology of stress ulcer disease. World J Surg. 1981 Mar;5(2):165-7.
[96] Leza & Menchen. Stress-induced deleterious consequences in the gastrointestinal tract. Curr Mol Med. 2008 Jun;8(4):244-6; page 4 (citing Choung & Talley, Epidemiology and clinical presentation of stress-related peptic damage and chronic peptic ulcer. Curr Mol Med. 2008 Jun;8(4):253-7)
[97] Leza & Menchen. Stress-induced deleterious consequences in the gastrointestinal tract. Curr Mol Med. 2008 Jun;8(4):244-6; pages 4-5 (citing a study by Gareau, et al. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008 Jun;8(4):274-8) See also, Lutgendorff, et al. The role of microbiota and probiotics in stress-induced gastrointestinal damage. Curr Mol Med. 2008 Jun;8(4):282-98 (finding probiotic microbe populations shrink due to stress, allowing pathogenic microbes to grow).

alters ion secretion.[98] In fact, "*H. pylori* infection and NSAIDs are independent risk factors for peptic ulcer disease that have additive or synergistic effects on adverse gastrointestinal outcomes[.]"[99]Studies have found the nervous system plays an important role in stress-induced ulceration. Dopamine receptor DA1 "produces gastroprotection by several mechanisms, at least one of which is by reducing gastric acid output."[100] Melatonin affects stress-induced ulceration through a mechanism involving the central nervous system,[101] and γ-aminobutyric acid (GABA) acts through peripheral receptors to reduce ulceration unrelated to gastric acid secretion.[102] Suppression of pentagastrin, an agonist of the cholecystokinin-B receptor which is expressed widely in the brain, stimulated gastric acid secretion by more than 90% prevented acid secretion and mucosal lesions.[103] Further, excessive peripheral sympathetic activity[104] and parasympathetic overactivity increase gastric acid output and contribute to stress-induced ulceration.[105] Increased vagus nerve activity was found to increase gastric choline acetyltransferase, acetylcholinesterase, and acetylcholine content, influencing gastric acid secretion.[106] Of interesting note, the vagus nerve, part of the parasympathetic system, was originally removed (vagotomy) as a treatment for peptic ulcers. The releasing factor for corticotrophin, a hormone and neurotransmitter, has been attributed as the main mediator of

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[98] Gareau, et al. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008 Jun;8(4):274-8; abstract. See also, Kitagawa, et al. Effects of water-immersion stress on gastric secretion and mucosal blood flow in rats. Gastroenterology. 1979 Aug;77(2):298-30 (suggesting that an elevation in gastric acid secretion without increase in mucosal blood flow causes gastric ulceration).

[99] Yuan, et al. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9; page 82, column 2.

[100] Glavin. Activity of selective dopamine DA1 and DA2 agonists and antagonists on experimental gastric lesions and gastric acid secretion. J Pharmacol Exp Ther. 1989 Nov;251(2):726-3; abstract.

[101] Kato, et al., Central effect of melatonin against stress-induced gastric ulcers in rats. NeuroReport. 1997 July 7;8(9): 2305-9; abstract.

[102] Miñano, et al., Effects of GABA on gastric acid secretion and ulcer formation in rats. Life Sciences. 1987 Sept 28;41(13): 1651-8; abstract.

[103] Garrick, et al., Cimetidine and rantidine protect against cold restraint-induced ulceration in rat by suppressing gastric acid secretion. Dig Dis Sci. 1987 Nov;32(11):1261-7.

[104] Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 July 28; 99:2416-2422; page 2416, column 1.

[105] Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 July 28; 99:2416-2422; page 2420, column 2; page 2421, column 2; abstract.

[106] Muramatsu, et al., Central regulation of gastric acetylcholine metabolism and acid output: analysis using stress and 2-deoxy-D-glucose administration in rats. Neurochem Int'l. 1986; 8(4): 553-8; abstract.

stress-induced damage,[107] and mast cells also influencing GI inflammation, evidencing that the brain-gut axis modulates the gastrointestinal immune system.[108]

Stress was also found to induce an increase in neutrophil infiltration in gastric mucosa, causing mucosal injury.[109] Inflammatory cytokines, such as IκBβ, NFκB, IL-1β, CINC-1, ICAM-1, and iNOS mRNA, increase linearly during stress. Neutralizing these cytokines reduced the activity of neutrophil reactive oxygen species, myeloperoxidase.[110] Stress induction increases reactive radicals causing protein oxidation and decreased glutathione content, with the severity of ulceration correlated with an increase in superoxide dismutase activity and decrease in peroxidase activity.[111] Further, studies have shown that specific A_{2A} agonists reduce production of pro-inflammatory cytokines, limit neutrophil activation, and inhibit stress-induced gastric inflammation;[112] and gastric prostacyclin inhibited indomethacin-induced decreases in mucosal blood flow and inhibited leukocyte accumulation.[113] Administration of catechin inhibits release of gastrin, somatostatin, and histamine; and provides a protective effect against ulceration.[114]

There is also evidence that stress-induced damage occurs, at least in part, due to localize gastric ischemia. Models of stress-induced ulcer show an association between alternating regions of high blood flow and low blood flow in the gastric corpus and gastric tissue damage.[115]

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[107] Leza & Menchen. Stress-induced deleterious consequences in the gastrointestinal tract. Curr Mol Med. 2008 Jun;8(4):244-6; page 5 (citing a study by Gareau, et al. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008 Jun;8(4):274-8).

[108] Caso, et al. The effects of physical and psychological stress on the gastrointestinal tract: lessons from animal models. Curr Mol Med. 2008 Jun;8(4):299-312; abstract.

[109] Hamaguchi, et al., Mechanisms and roles of neutrophil infiltration in stress-induced gastric injury in rats. Dig Dis Sci. 2001 Dec;46(12):2708-15; abstract.

[110] Jia, et al., Sustained activation of nuclear factor-kappaB by reactive oxygen species is involved in the pathogenesis of stress-induced gastric damage in rats. Crit Care Med. 2007 Jun;35(6):1582-91; abstract.

[111] Das, et al., Hydroxyl radicalis the major causative factor in stress-induced gastric ulceration. Free Radical Biol and Med. 1997; 23(1): 8-18; abstract.

[112] Odashima, et al., Selective adenosine A_{2A} receptor agonist, ATL-146e, attenuates stress-induced gastric lesions in rats. J Gastroenterol Hepatol. 2005 Feb;20(2):275-80; abstract.

[113] Harada, et al., Gastric prostacyclin (PGI2) prevents stress-induced gastric mucosal injury in rats primarily by inhibiting leukocyte activation. Prostaglandins Other Lipid Mediat. 1999 Jul;57(5-6):291-303; abstract.

[114] Sato, et al., The protective effect of catechin on gastric mucosal lesions in rats, and its hormonal mechanisms. J Gastronent. 2002 Feb; 37(2): 106-11; abstract.

[115] Livingston, et al., Heterogeneous distribution of gastric mucosal blood flow with restraint stress in the rat. Digestive Diseases and Sciences. 1993 Jul; 38(7): 1233-1242; abstract.

Administration of taurocholate uncouples oxidative phosphorylation of gastric mucosal mitochondria and inhibits ATPase, causing damage to the mucosa.[116]

As can be seen above, the art does not consider stress-induced ulceration to be the same as NSAID-induced ulceration. It is submitted that there are significant differences in the causes of damage, such as blocking COX-1 and COX-2, and other prostaglandin-independent mechanisms like H_2S and NO reduction for NSAID-induced ulcers,[117] or mucosal inflammation and excessive peripheral sympathetic activity[118] and parasympathetic overactivity for stress-induced ulcers. Likewise, cNOS activity has been found useful in addressing NSAID-induced ulcers, whereas iNOS has been seen to impact stress-induced ulcers. It is therefore submitted that one of skill in the art would not find it obvious to combine treatments for stress-induced ulcers for the treatment of NSAID-induced ulcers.

Furthermore, Applicant respectfully points out that MPTP is a neurotoxin precursor, not a therapeutic agent. MPTP is metabolized into 1-methyl-4-phenylpyridinium (MPP+) by MAO-B, which kills dopamine-producing neurons by interfering with complex I of the electron transport chain and causing a buildup of free radicals.[119] Assertions of the perspective of a person of ordinary skill must be used in the obviousness inquiry, and require sufficient explanation such as providing any evidentiary support or reasoning for why a person of ordinary skill in the field of the invention would have deemed it obvious to select and combine various steps from different references, in the manner of the applicant.[120] It is respectfully submitted that the Office has not articulated how the results from a neurotoxin, which destroy dopamine-producing neurons, are related to ulceration caused by anti-inflammatory drugs.

Applicant resubmits the combination of *Glavin, et al.* and *Lianping, et al.* fail to obviate the claimed invention as the references do not disclose the elements claimed. The courts have

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[116] Menguy & Masters, Mechanism of stress ulcer. Digestive Diseases and Sciences. 1976 Dec; 21(12): 1001-1007; abstract.
[117] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3, page 2, column 1; page 3, Table 1.
[118] Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 July 28; 99:2416-2422; page 2416, column 1.
[119] Richardson, et al., Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicol Sci. 2005; 88(1): 193-201; 193, column 2. http://en.wikipedia.org/wiki/MPTP (last accessed June 30, 2010).
[120] *In re Vaidyanathan*, 2010 WL 2000682, page 8 (Fed. Cir. 2010) (not precedential).

consistently held the claimed invention must be considered as a whole when determining obviousness.[121] Claim 1, as amended provides:

> A method of preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs, comprising:
>
> administering to a subject an effective amount of MAO inhibitor;
> wherein the anti-inflammatory drug and MAO inhibitor are chemically linked, physically mixed or administered separately.

"Ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language … and considering both the invention and the prior art as a whole.[122] As noted by the Office, *Glavin, et al.* and *Lianping, et al.* focus on dopamine levels,[123] and do not disclose a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs comprising administration of an MAO inhibitor.[124] All the limitations of a claim must be considered when weighing the differences between the claimed invention and the prior art in determining the obviousness of a process or method claim.[125] However, the references fail to discuss anti-inflammatory agents or indicate any relevance to anti-inflammatory agents. Moreover, it is submitted that the Office's rationale to link MPTP-depletion induced ulceration and stress-induced ulceration, that the references both show gastrointestinal protective effect, is not sufficient given the drastic differences between causative effect and treatment between stress-induced ulceration and anti-inflammatory damage, as discussed above.

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[121] See, MPEP 2141.02 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). See also, *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983).
[122] MPEP 2141(II)(B).
[123] Page 9 of the final Office Action, dated April 1, 2010, page 10 of the non-final Office Action, dated Jan. 13, 2009. See also, Lianping Xing, J. Seaton, G. Kauffman, "Monoamine Oxidase B Inhibition Reduces Gastric Mucosal Blood Flow, Basal Acid Secretion, and Cold Water Restrain-Induced Gastric Mucosal Injury in Rats," Digestive Dis. And Sci., Jan. 1990; 35(1):61-65, page 61, abstract (DA and NE concentrations in nucleus accumbens is associated with restraint-induced mucosal injury), page 64, column 2 (data indicates central inhibition of MAO-B increases DA and NE concentrations, and indicates central DA and NE are involved in gastric mucosal control); G. Glavin, A. Dugani, C. Pinsky, "L-Deprenyl Attenuates Stress Ulcer Formation in Rats," Neurosci. Ltrs. 1986; 70:379-381, page 380-381.
[124] Page 9 of the final Office Action, dated April 1, 2010.
[125] MPEP 2116.01 (citing also to MPEP 2143.04)

The combination of *Glavin, et al.* (Neurosci. Ltrs., 1986) and *Lianping, et al.* fail to obviate the claimed invention, because a *prima facie* case of obviousness has not been established. The Office found that

> [t]he protective gastrointestinal effect is disclosed in both references. It would have been obvious to employ the MAO inhibitors to provide a protective effect to the gastrointestinal mucosa when NSAIDs are administered.[126]

As noted above, the causes and type of ulceration differs between NSAID-induced ulcers and stress-induced ulcers. Because the references do not address the use of MAO inhibitors with anti-inflammatory drugs, not all the limitations of the claim are addressed by the references.

The Office's findings, stating that the references show protective gastrointestinal effects, do not provide a reason why one would consider articles disclosing stress-induced and dopamine-induced ulceration to obviate the claimed invention. Applicant also respectfully points out that there is a link between the parasympathetic nervous system and stress-induced ulcerations,[127] therefore there is a link between brain function and stress-induced ulceration as discussed above. Assertions of the perspective of a person of ordinary skill must be used in the obviousness inquiry, and require sufficient explanation such as providing any evidentiary support or reasoning for why a person of ordinary skill in the field of the invention would have deemed it obvious to select and combine various steps from different references, in the manner of the applicant.[128]

> [W]hether or not stated explicitly, the perspective of a person of ordinary skill must frame the obviousness inquiry, and assertions of what such a person of ordinary skill would have found to be obvious require sufficient explanation to permit meaningful appellate review… [such as] providing any evidentiary support or reasoning for why a person of ordinary skill in the field of the invention would have deemed it obvious to select and combine various steps from different references, in the manner of the applicant.[129]

The Office's findings state that according to *Glavin* there is a relationship between dopamine deficiency and ulceration, and that L-deprenyl can be used to prevent ulceration associated with

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[126] Page 10 of the final Office Action, dated April 1, 2010.
[127] Caso, et al., The effects of physical and psychological stress on the gastrointestinal tract: lessons from animal models. Curr Mol Med. 2008 Jun;8(4):299-31, abstract; Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 Dec;99(6):2416-22. Epub 2005 Jul 28;abstract; page 2416, columns 1-2.
[128] *In re Vaidyanathan*, 2010 WL 2000682, page 8 (Fed. Cir. 2010) (not precedential).
[129] *In re Vaidyanathan*, 2010 WL 2000682, page 8 (Fed. Cir. 2010) (not precedential).

such deficiency.[130] The Office also noted that *Lianping* discusses utilizing MAO inhibitors to reduce stress-induced ulceration.[131]

Applicant asserts that the references fail to disclose the compositions for use with NSAIDs. Further, there is no evidentiary support or rationale to show how one skilled in the art would find the use compositions for different ailments, such as stress-induced ulceration, to obviate a method of preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs. Obviousness must be determined by comparing the differences between the claimed invention and prior art.[132] In *In re Hirao*, a three step process was determined nonobviousness over a two step process teaching a similar method, as the prior art, when compared to the claimed invention as a whole, did not obviate the invention.[133] It is submitted the Office does not show how one of skill in the art would find these references obviate a method drawn to treating NSAID-induced ulceration, as provided in the claims. As noted above, NSAID-induced ulceration differs from stress-induced ulceration, which the art found may be linked to central nervous system's parasympathetic system.[134] Conversely, NSAID ulceration is caused by localized damage from the NSAID drug.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious"[135] The Office stated that ""[o]ne of ordinary skill in the art would have been capable of applying this known technique to a known method that was ready for improvement and the *results would have been predictable* to one of ordinary skill in the art."[136] The present invention provides cytoprotection to GI mucosa[137] through MAO inhibition by effects such as free radical scavenging, antioxidant properties, stimulation of antioxidant enzyme expression, endothelial protection, vasodilation, enhanced

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[130] Page 9 of the final Office Action, dated April 1, 2010.
[131] Page 9 of the final Office Action, dated April 1, 2010.
[132] MPEP 2141.02(I).
[133] *Id.* (citing *In re Hirao*, 535 F.2d 67, 190 U.S.P.Q. 15 (CCPA 1976)).

[134] Caso, et al., The effects of physical and psychological stress on the gastrointestinal tract: lessons from animal models. Curr Mol Med. 2008 Jun;8(4):299-31, abstract; Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 Dec;99(6):2416-22. Epub 2005 Jul 28;abstract; page 2416, columns 1-2.

[135] MPEP 2142.
[136] Page 11 of the non-final Office Action, dated Jan. 13, 2009 (emphasis added).
[137] See, page 18 of the Application ("the cytoprotective effect of MAO inhibitors in preventing and/or reversing the NSAID toxicity may be mediated by a combination of several cytoprotective actions[.]")

blood flow, and stimulation of nitrogen oxide synthase.[138] Conversely, studies of existing cytoprotective anti-ulcer drugs have shown the drugs are "ineffective in preventing ulceration."[139] The Office's findings relating to MPTP-depletion induced ulceration and stress-induced ulceration do not show an adequate link to NSAID-induced ulceration, due to the differences in etymology and treatment. Therefore, Applicant submits the failure of the references to disclose the use of anti-inflammatory drugs is fatal to the obviousness determination.

The combination of *Glavin, et al.* and *Lianping, et al.* fail to obviate the present invention because the combined references fail to disclose the elements of the claimed invention. Further, a *prima facie* case of obviousness has not been established as the rationale used to support the obviousness finding relies on the predictability in the art, which the Office has also found to be lacking. Accordingly, Applicant respectfully requests the 35 U.S.C. § 103(a) rejection of claims 1-5, 7, 17 and 20 be withdrawn.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

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[138] Pages 17-18 of the Application.
[139] Nakashima, S., et al., Usefulness of anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low doses of aspirin, World J. Gastroenterol. 2009 Feb 14;15(6):727-31, page 1, column 2.

CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

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Lauren Reeves